IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Surmeier, et al.	Group No.:	1635
Serial No.:	10/761,557	Examiner:	Chong
Filed:	01/21/2004		
Entitled:	**Manipulation of Neuronal Ion Channels**		

DECLARATION OF D. JAMES SURMEIER, Ph.D. UNDER 37 CFR § 1.132

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CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted tp the United States Patent and Tradmeark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. Section 1.6(a)(4).

Dated: August 6, 2008 By: /Jasmine M. Stansberry/

Examiner Chong:

I, D. James Surmeier, Ph. D. hereby declare and state, under penalty of perjury, that:

1. I am one of the inventors of U.S. patent application 10/761,557 covering neuronal ion channels and manipulation of neuronal ion channels. I have worked in the field of physiology and have numerous publications in this field.

2. Several studies have implicated Kv3 family potassium channels in producing ionic currents that enable fast-spiking in neurons. Kv3 channels are multimeric proteins consisting of four transmembrane domains that are coded for by distinct genes. There are four genes in the Kv3 family that code for Kv3.1-4 subunits. In heterologous expression systems, homomeric Kv3.1-3 channels exhibit rapid opening with depolarization and little or no inactivation with sustained depolarization. This gating property is typical of delayed rectifier channels underlying spike repolarization.

3. In contrast, homomeric Kv3.4 channels are rapidly inactivating, unlike delayed rectifier channels in fast spiking neurons. Moreover, co-expression of the only available splice variant of the Kv3.4 subunit at that time with Kv3.1 subunits failed to produce a channel with properties that were distinguishable from homomeric Kv3.1 channels. As a consequence, there was very little work on Kv3.4 subunits because they appeared not to be important in determining the properties of Kv3 channels underlying fast spiking behavior.

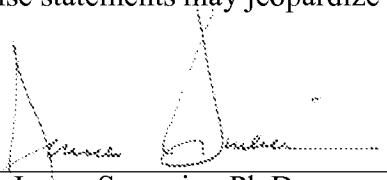
4. Our work, found in the present patent application and first published in Nature Neuroscience in 2003 (Baranauskas et al.), changed this picture. First, we showed that while homomeric Kv3.1 channels open rapidly with depolarization, they did so at more positive membrane potentials than native channels, indicating that there was a modifying protein expressed with this native channel. Homomeric channels were capable of repolarizing spikes, they were not as **efficient** as native channels. We then showed that a distinctive splice variant of the Kv3.4 subunit was expressed in fast spiking neurons found in several regions of the brain (hippocampus, cortex, basal ganglia).

5. Furthermore, we showed that co-expression of this distinctive subunit altered the properties of Kv3.1 channels, making them indistinguishable in their gating properties to those found in native fast spiking neurons and increasing their **efficiency** in promoting rapid spike repolarization and fast spiking. Thus, our work showed that contrary to the prediction of the published literature that Kv3.4 subunits were not important to the ability of neurons to spike at high frequencies – in fact, they were important.

6. Our therapeutic strategy in, for example, Parkinson's disease is based upon this ability of Kv3.4 subunits to modify the **efficiency** of Kv3 channels in repolarizing spikes and promoting fast spiking. By reducing the availability of Kv3.4 subunits, the efficiency of the Kv3 channels expressed in globus pallidus and subthalamic nucleus neurons is reduced. This results in broader spikes and a diminished capacity to spike at high frequencies. This strategy does not target Kv3.1-3 subunits and therefore should not reduce the overall density of Kv3 channels in either type of neuron. Rather, by simply reducing the efficiency of these channels, the therapy specifically reduces or eliminates what is generally thought to be the pathological aspect of the spiking of these neurons in the Parkinson's disease state – very high spiking rates or 'bursts'. This is accomplished without eliminating spiking in general or the ability to spike at lower rates that are crucial to the normal function of these neurons. This is not an outcome that can be achieved by targeting Kv3 channels more broadly or by reducing the expression level of Kv3.1-3 subunits.

7. Prior to the present invention, it would not have been obvious to arrive at the presently claimed invention because one would not have been able to predict that Kv3.4 subunits were important or relevant to the ability of neurons to spike at high frequencies, and thus would not have been motivated to inhibit their activity in order to decrease spiking at high frequencies nor able to predict any benefit of such inhibition.

8. I declare that all statements made herein are of my own knowledge and are true, and further that those statements are made with the knowledge that willful false statements and the like so mare are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the patent application or any patent issuing therefrom.



D. James Surmeier, Ph.D.

August 5, 2008
Date